



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2014-P-0377]

Determination that ACTHAR GEL SYNTHETIC (Seractide Acetate) Injection, 80

Units/Milliliter and 40 Units/Milliliter, was Withdrawn from Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or we) has determined that ACTHAR GEL SYNTHETIC (seractide acetate) injection, 80 units/milliliter (mL) and 40 units/mL, was withdrawn from sale for reasons of safety or effectiveness. The Agency will not accept or approve abbreviated new drug applications (ANDAs) for seractide acetate injection, 80 units/mL and 40 units/mL.

FOR FURTHER INFORMATION CONTACT: David E. Markert, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6222, Silver Spring, MD 20993-0002, 301-796-0752.

SUPPLEMENTARY INFORMATION:

I. Background

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active

ingredient in the same strength and dosage form as the “listed drug,” which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA).

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the “Approved Drug Products With Therapeutic Equivalence Evaluations,” which is known generally as the “Orange Book.” Under FDA regulations, drugs are removed from the list if the Agency withdraws or suspends approval of the drug’s NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

A person may petition the Agency to determine, or the Agency may determine on its own initiative, whether a listed drug was withdrawn from sale for reasons of safety or effectiveness. This determination may be made at any time after the drug has been withdrawn from sale, but must be made prior to approving an ANDA that refers to the listed drug (21 CFR 314.161). FDA may not approve an ANDA that does not refer to a listed drug.

ACTHAR GEL SYNTHETIC (seractide acetate) injection, 80 units/mL and 40 units/mL was the subject of NDA 017861, which was held by Armour Pharmaceutical Co. (Armour), and initially approved on February 21, 1978. ACTHAR GEL SYNTHETIC is indicated for diagnostic testing of adrenocortical function. The labeling also provides that ACTHAR GEL SYNTHETIC may be employed in the following disorders:

ENDOCRINE DISORDERS: Nonsuppurative thyroiditis; Hypercalcemia associated with cancer.

NERVOUS SYSTEM DISEASES: Acute exacerbations of multiple sclerosis.

RHEUMATIC DISORDERS: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: Psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy); ankylosing spondylitis; acute and subacute bursitis; acute non-specific tenosynovitis; acute gouty arthritis; post-traumatic arthritis; synovitis of osteoarthritis; epicondylitis.

COLLAGEN DISEASES: During an exacerbation or as maintenance therapy in selected cases of: Systemic lupus erythematosus; systemic dermatomyositis (polymyositis); acute rheumatic carditis.

DERMATOLOGIC DISEASES: Pemphigus; bullous dermatitis herpetiformis; severe erythema multiforme (Stevens-Johnson syndrome); exfoliative dermatitis; severe psoriasis; severe seborrheic dermatitis; mycosis fungoides.

ALLERGIC STATES: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment--seasonal or perennial allergic rhinitis; bronchial asthma; contact dermatitis; atopic dermatitis; serum sickness.

OPHTHALMIC DISEASES: Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: Allergic conjunctivitis; keratitis; herpes zoster ophthalmicus; iritis and iridocyclitis; diffuse posterior uveitis and choroiditis; optic neuritis; sympathetic ophthalmia; chorioretinitis; anterior segment inflammation; allergic corneal marginal ulcers.

RESPIRATORY DISEASES: Symptomatic sarcoidosis; Loeffler's syndrome not manageable by other means; berylliosis; fulminating or disseminated pulmonary tuberculosis when used concurrently with anti-tuberculous chemotherapy; aspiration pneumonitis.

HEMATOLOGIC DISORDERS: Acquired (autoimmune) hemolytic anemia; secondary thrombocytopenia in adults; erythroblastopenia (RBC anemia); congenital (erythroid) hypoplastic anemia.

NEOPLASTIC DISEASES: For palliative management of: Leukemias and lymphomas in adults; acute leukemia of childhood.

EDEMATOUS STATE: To induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.

GASTROINTESTINAL DISEASES: To tide the patient over a critical period of the disease in: Ulcerative colitis; regional enteritis.

MISCELLANEOUS: Tuberculous meningitis with subarachnoid block or impending block when concurrently accompanied by appropriate anti-tuberculous chemotherapy; trichinosis with neurologic or myocardial involvement.

Armour never marketed ACTHAR GEL SYNTHETIC (seractide acetate) injection, 80 units/mL and 40 units/mL. In previous instances (see, e.g., 72 FR 9763, March 5, 2007 and 61 FR 25497, May 21, 1996), the Agency has determined that for purposes of §§ 314.161 and 314.162, never marketing an approved drug product is equivalent to withdrawing the drug from sale. FDA withdrew approval of the NDA for ACTHAR GEL SYNTHETIC in 2014 because Armour had repeatedly failed to file annual reports for the application (79 FR 68454, November 17, 2014).

Hyman, Phelps & McNamara, P.C., submitted a citizen petition dated April 1, 2014 (Docket No. FDA-2014-P-0377), under 21 CFR 10.30, requesting that the Agency determine whether ACTHAR GEL SYNTHETIC (seractide acetate) injection, 80 units/mL and 40 units/mL, was withdrawn from sale for reasons of safety or effectiveness.

II. Response to Citizen Petition

We have carefully reviewed the citizen petition (and comments submitted to the docket); our records for ACTHAR GEL SYNTHETIC (seractide acetate) injection, 80 units/mL and 40 units/mL; the scientific literature on seractide acetate; and other relevant information. Based on that review, and for the reasons set forth in this section, we have concluded that additional studies of safety would be necessary before ACTHAR GEL SYNTHETIC could be considered for introduction to the market today. Consequently, FDA has determined under § 314.161 that ACTHAR GEL SYNTHETIC (seractide acetate) injection, 80 units/mL and 40 units/mL, was withdrawn for reasons of safety.¹

The labeling for ACTHAR GEL SYNTHETIC describes the product as “a highly purified synthetic polypeptide containing thirty-nine amino acids in the sequence described for human corticotropin by Lee, T.H.; Lerner, A.B.; and Buettner-Janusch, Vina (J. Biol Chem, 236:2970-2974, Nov. 1961)” (Refs. 1 and 2). At the time of ACTHAR GEL SYNTHETIC’s approval, FDA believed the amino acid sequence described by Lee et al. was the correct sequence for human corticotropin and, therefore, that ACTHAR GEL SYNTHETIC was identical to human corticotropin.² However, since approval, the Agency has learned that ACTHAR GEL SYNTHETIC is not identical to the human corticotropin sequence. We now know that the amino acid sequence described by Lee et al. is a deamidated version of human corticotropin that differs from full length human corticotropin at four positions.³

¹ In light of this conclusion, it is unnecessary for us to determine whether ACTHAR GEL SYNTHETIC was also withdrawn from sale for reasons of effectiveness. This notice does not address the effectiveness of ACTHAR GEL SYNTHETIC for its labeled indications.

² The Agency’s Institutional Summary of Basis of Approval (Ref. 3) describes ACTHAR GEL SYNTHETIC as “a synthetic peptide of 39 amino acids identical with that of natural human” corticotropin.

³ The record for human pro-opiomelanocortin preproprotein in the National Center for Biotechnology Information’s “Protein” database (Reference Sequence NP_000930.1) contains the correct amino acid sequence for human corticotropin. The record is available at the following URL: https://www.ncbi.nlm.nih.gov/protein/NP_000930.1.

The fact that ACTHAR GEL SYNTHETIC has a different amino acid sequence from human corticotropin raises significant safety concerns. Due to its different amino acid sequence, ACTHAR GEL SYNTHETIC might have a structure or function that is not recognized as endogenous by the immune system. ACTHAR GEL SYNTHETIC thus poses a higher risk of immunogenicity than a synthetic peptide product that is, in fact, identical to human corticotropin. The health consequences of immunogenicity range from subacute, minor reactions to severe, even deadly, reactions (e.g., anaphylaxis). In addition, frequent stimulation of the immune system could produce antibodies that cross-react with human corticotropin and other closely related endogenous peptides, resulting in the loss of those peptides' physiological functions. Such an effect could last long after treatment with ACTHAR GEL SYNTHETIC has stopped.

The safety concerns noted in this section have not been adequately investigated. ACTHAR GEL SYNTHETIC was studied in two clinical trials in 51 healthy adult men between 21 and 54 years old. Although no unusual adverse effects were reported during these trials, the trials did not assess the impact of immunogenicity on safety. Nor were they designed to assess immunogenicity. Moreover, because ACTHAR GEL SYNTHETIC was never marketed, the Agency has no postmarketing safety data or information confirming that the product is safe for human use, notwithstanding the differences between ACTHAR GEL SYNTHETIC's amino acid sequence and that of human corticotropin. Given the lack of any premarket or postmarket immunogenicity safety data, FDA cannot conclude that ACTHAR GEL SYNTHETIC would be safe for human use if it were introduced to the market today.

The sequence described by Lee et al. differs from the correct sequence at positions 25-27 and 30.

Accordingly, the Agency will remove ACTHAR GEL SYNTHETIC (seractide acetate) injection, 80 units/mL and 40 units/mL, from the list of drug products published in the Orange Book. FDA will not accept or approve ANDAs that refer to this drug product.

III. References

The following references have been placed on display in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <https://www.regulations.gov>.

1. Armour Pharmaceutical Co., “ACTHAR[®] Gel Synthetic (SERACTIDE ACETATE), Synthetic Corticotropin,” Product Labeling, 1979.
2. Lee, T. H., A. B. Lerner, and V. Buettner-Janusch, “On the Structure of Human Corticotropin (Adrenocorticotrophic Hormone),” The Journal of Biological Chemistry, vol. 236, pp. 2970-2974, 1961.
3. FDA, “Seractide Acetate: Institutional Summary of Basis of Approval,” August 22, 1977.

Dated: January 13, 2017.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2017-01249 Filed: 1/19/2017 8:45 am; Publication Date: 1/23/2017]